

PATENT COOPERATION TREATY

JF/OL

From the INTERNATIONAL SEARCHING AUTHORITY

To:
MARY E. BAK
HOWSON AND HOWSON
321 NORRISTOWN ROAD, SUITE 200
SPRING HOUSE CORPORATE CENTER, P.O. BOX 457
SPRING HOUSE, PA 19477

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference RTS-0678WO	Date of mailing (day/month/year) 23 MAR 2006
International application No. PCT/US04/24384	International filing date (day/month/year) 18 August 2004 (18.08.2004)
Applicant ISIS PHARMACEUTICALS INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70.

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

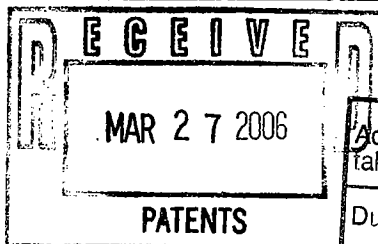
In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Jon B. Ashen Telephone No. 703-308-1235
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Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)



ISIS DOCKETING

Action to be taken:	Article 19 amend	
Due Date(s):	5/23/06	5/23/06
PCM Entry by:	SA	SA

counsel
copied
more

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference RTS-0678WO	FOR FURTHER ACTION		see Form PCT/ISA/220 as well as, where applicable, item 5 below
International application No. PCT/US04/24384	International filing date (day/month/year) 18 August 2004 (18.08.2004)	(Earliest) Priority Date (day/month/year) 18 August 2003 (18.08.2003)	
Applicant ISIS PHARMACEUTICALS INC.			

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

a. With regard to the language, the international search was carried out on the basis of:



the international application in the language in which it was filed.



a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☒ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box No. II)

3. ☒ Unity of invention is lacking (See Box No. III)

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____



as suggested by the applicant.



as selected by this Authority, because the applicant failed to suggest a figure.



as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/24384

Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

a. type of material



a sequence listing



table(s) related to the sequence listing

b. format of material



on paper



in electronic form

c. time of filing/furnishing



contained in the international application as filed



filed together with the international application in electronic form



furnished subsequently to this Authority for the purposes of search

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/24384

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 1-16, 21, 40-45 and 58 (SEQ ID NOS: 21, 35 and 65)
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

- Remark on Protest**
- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/24384

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) : C07H 21/04

US CL : 536/24.5

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/24.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,605,451 (MARMARO ET AL.) 12 August 2003 (12.08.2003)	1, 4-5, 8, 21 and 43
Y		6-7, 9-16, 41-42, 44-45
Y	US 5,998,148 (BENNETT ET AL.) 7 December 1999 (07.12.1999)	6-7, 9-16, 41-42, 44-45

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

04 November 2005 (04.11.2005)

Date of mailing of the international search report

23 MAR 2006

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US

Commissioner for Patents

P.O. Box 1450

Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Authorized officer

Jon B. Ashen

Telephone No. 703-808-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/24384

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups 1-86, claim(s) 1-16, 21, 40-45 and 58, drawn to an antisense compound 13 to 40 nucleobases in length targeted to a nucleic acid molecule encoding diacylglycerol acyltransferase 2 wherein said compound comprises a sequence selected from the group consisting of the 86 different SEQ ID NOs: as listed in claims 2 and 40.

Group 87, claim(s) 17, 22-39 and 48-57, drawn to a method of inhibiting the expression of diacylglycerol acyltransferase 2 in cells or tissues or in an animal comprising contacting or administering the compound of claim 1.

Group 88, claim(s) 18 and 19, drawn to a method of screening for a modulator of diacylglycerol acyltransferase 2.

Groups 89-91, claim(s) 20, drawn to a method for identifying the presence of diacylglycerol acyltransferase 2 in a sample using SEQ ID NO: 6, SEQ ID NO: 7 or SEQ ID NO: 8.

Groups 92-97, claim(s) 1 and 58-65 drawn to an antisense compound that comprises a sequence selected from the group of SEQ ID NOs: 238, 241-243, 251 and 252.

Group 98, claim(s) 46, 47, and 66-70, drawn to the use of a compound according to claim 1 or claim 4 in the manufacture or preparation of a medicament.

The inventions listed as Groups 1-98 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

This international searching authority has found 98 inventions claimed in the international application covered by the claim(s) indicated below:

Claims 2, 20, 40 and 65 specifically claim SEQ ID NOs: as listed that are targeted to and modulate the expression of diacylglycerol acyltransferase 2.

This international searching authority considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

According to the guidelines in Section (f)(i)(a) of Annex B of the PCT Administrative Instructions, the special technical feature as defined by PCT Rule 13.2 shall be considered to be met when all the alternatives of a Markush-group are of similar nature. For chemical alternatives, such as the claimed polynucleotide sequences, the Markush group shall be regarded as being of similar nature when:

(A) all alternatives have a common property or activity and

(B)(1) a common structure is present, i.e., a significant structure is shared by all of the alternatives or

(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to an art recognized class of compounds in the art to which the invention pertains.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/24384

The instant nucleotide sequences claimed, that are antisense, probe and primer sequences, are considered to be each separate inventions for the following reasons:

The sequences do not meet the criteria of (A), common property or activity or (B)(2), art recognized class of compounds. Although the antisense sequences of the instant application all target and modulate expression of the diacylglycerol acyltransferase 2 gene, each antisense sequence behaves in a different way in the context of the claimed invention. Each sequence targets a different and specific region of diacylglycerol acyltransferase 2 and each sequence decreases the expression of the gene to varying degrees (as shown in Tables 1-23, throughout). In particular regards to the probes and primers listed in claim 20, each primer or probe also targets a different and specific region of diacylglycerol acyltransferase 2. Each member of the class of antisense oligonucleotides, probes or primers cannot be substituted, one for the other, with the expectation that the same intended result would be achieved.

Further, although the instant antisense, probe and primer sequences target the same gene, the sequences do not meet the criteria of (B)(1), as they do not share, one with another, a common core structure. Accordingly, unity of invention between the nucleotide sequences of the antisense, probes and primers claimed in the instant application is lacking and each nucleotide sequence claimed is considered to constitute a special technical feature.

For PCT's: If the polynucleotide sequences of the instant invention are recited in the first claimed invention, Applicants will obtain a search of the first sequence listed in the claim. For every other sequence applicants wish to have searched, applicants need to elect the sequence and pay an additional fee.

If the sequences are recited in the second or subsequent claimed invention, Applicants will need to elect the group and pay the fee to obtain a search of the first sequence listed in the claims encompassed by the second or subsequent group. For every other sequence in the second/subsequent group that applicants wish to have searched, applicants need to elect the sequence and pay an additional fee.

The special technical feature of groups 1-86 is an antisense compound that comprises a specific SEQ ID NO.; said SEQ ID NO: being a nucleotide sequence selected from the group consisting of the 86 different SEQ ID NOs: as listed in claims 2 and 40.

The special technical feature of group 87 is a method of inhibiting the expression of diacylglycerol acyltransferase 2 in cells or tissues or in an animal comprising contacting or administering the compound of claim 1.

The special technical feature of group 88 is a method of screening for a modulator of diacylglycerol acyltransferase 2.

The special technical feature of groups 89-91 is a method for identifying the presence of diacylglycerol acyltransferase 2 in a sample using SEQ ID NO: 6, SEQ ID NO: 7 or SEQ ID NO: 8.

The special technical feature of groups 92-97 is an antisense compound that comprises a specific SEQ ID NO.; said SEQ ID NO: being a nucleotide sequence selected from the group consisting of SEQ ID NOs: 238, 241-243, 251 and 252.

The special technical feature of group 98 is the use of a compound according to claim 1 or claim 4 in the manufacture or preparation of a medicament.

Continuation of B. FIELDS SEARCHED Item 3:

STIC: SEQ ID NO: 21, 35 and 65

EAST

STN (medline, biosis, embase, caplus)

Search Terms: diacylglycerol acyltransferase 2, antisense

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MARY E. BAK
HOWSON AND HOWSON
321 NORRISTOWN ROAD, SUITE 200
SPRING HOUSE CORPORATE CENTER, PO. BOX 457
SPRING HOUSE, PA 19477

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference RTS-0678WO		Date of mailing (day/month/year) 23 MAR 2006
International application No. PCT/US04/24384		International filing date (day/month/year) 18 August 2004 (18.08.2004)
International Patent Classification (IPC) or both national classification and IPC IPC(2): C07H 21/04 and US CL: 536/24.5		Priority date (day/month/year) 18 August 2003 (18.08.2003)
Applicant ISIS PHARMACEUTICALS INC.		

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(h) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Date of completion of this opinion 04 November 2005 (04.11.2005)	Authorized officer Jon B. Ashen Telephone No. 703-308-1235
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Form PCT/ISA/237 (cover sheet) (April 2005)

ISIS DOCKETING

Action to be taken:	Response	
Due Date(s):	4/23/06	4/28/06
PCT Entry by:	CO	Date: 3/29/06

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US04/24384

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

- ☒ a sequence listing
☐ table(s) related to the sequence listing

b. format of material

- ☒ on paper
☒ in electronic form

c. time of filing/furnishing

- ☒ contained in the international application as filed.
☒ filed together with the international application in electronic form.
☐ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US04/24384

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☒ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

☐ complied with

☒ not complied with for the following reasons:

See the lack of unity section of the International Search Report (Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:

☐ all parts.

☒ the parts relating to claims Nos. 1-16, 21, 40-45 and 58 (SEQ ID NOS: 21, 35 and 65) *SEQ ID NOS: 284, 288, 353, 373 and 410 were not searched because these sequences do not appear in the instant claims and no search can be performed on subject matter that is not claimed.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US04/24384

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>2-3, 40 and 58</u>	YES
	Claims <u>1, 4-5, 8, 21, 43</u>	NO
Inventive step (IS)	Claims <u>2-3, 40 and 58</u>	YES
	Claims <u>1, 4-16, 21, 41-45</u>	NO
Industrial applicability (IA)	Claims <u>1-16, 21, 40-45 and 58</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Claims 1, 4-5, 8, 21 and 43 lack novelty under PCT Article 33(2) as being anticipated by Marmaro et al. (US 6,605,451). Marmaro et al. disclose SEQ ID NO: 38, an 18 nucleobase DNA oligonucleotide is 72% complementary to the coding region of a nucleic acid molecule encoding diacylglycerol acyltransferase 2 (dgat2) (col. 10, table 1). Absent evidence to the contrary, SEQ ID NO: 38 is an antisense oligonucleotide targeted to dgat2. SEQ ID NO: is disclosed as comprised in a kit (col. 4, lines 41-50).

Claims 6-7, 9-16, 41-42 and 44-45 lack an inventive step under PCT Article 33(3) as being obvious over Marmaro et al. in view of Bennett et al. The teachings of Marmaro et al. are relied upon as above. Marmaro et al. do not teach RNA or chimeric oligonucleotides (claims 6-7), 80%, 90%, 95% or 99% limitations on complementarity (claims 9-12), modified internucleoside linkages, sugars or bases (claims 15-18) or antisense targeted to the 5' UTR, the start region, the stop region or the 3' UTR of a nucleic acid molecule encoding SGLT2 (claims 41-42 and 44-45). Bennett et al. provide an extensive disclosure of antisense technology, including regions that are suitable for targeting by antisense (including the 5' UTR, start and stop regions and 3' UTR; see cols. 3-4), modifications that are desirable to make to antisense oligonucleotide to increase stability and nuclease resistance, including phosphorothioate internucleoside linkages 2-O-methyl sugar modifications and 5-methylcytosine base modifications (see cols. 6-9). Bennett et al. teach both RNA and chimeric antisense oligonucleotides (see col. 10) and that antisense oligonucleotides are able to inhibit gene expression with exquisite specificity and are often used by those of ordinary skill in the art to elucidate the function of particular genes, to distinguish functions between different genes and are harnessed by those of skill in the art for use in therapeutic purposes (col. 5, lines 25-55). Bennett et al. also teach that an oligonucleotide need not be 100% complementary to specifically hybridize and function as antisense (col. 5, lines 4-23). Therefore, because antisense to dgat2 was known in the prior art as taught by Marmaro et al. and because Bennett et al. provide an extensive disclosure of antisense technology, including RNA and chimeric oligonucleotides, target nucleic acid regions and desired oligonucleotide modifications for increasing stability and nuclease resistance, one of ordinary skill in the art would not consider it inventive to combine the teachings of Marmaro et al. and Bennett et al. to formulate the instantly claimed oligomeric compound as an antisense oligonucleotide targeted to dgat2 and would have considered the determination of the sufficient degree of complementarity required for a given antisense oligonucleotide to be specifically hybridizable, to be design choice. One of ordinary skill in the art would have found it obvious and motivated by the disclosure of Bennett et al. to modify the antisense oligonucleotide of Marmaro et al. and would have expected success because the modifications disclosed by Bennett et al. were known to be successful modifications in the prior art.

Claims 2-3, 40 and 58 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an antisense compound 13-40 nucleobases in length that comprises SEQ ID NO: 21, 35 or 65.

Claims 1-16, 21, 40-45 and 58 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US04/24384

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 1-16, 21, 40-45 and 58 are unclear under PCT Rule 6 (i.e., 112 2nd paragraph indefiniteness). All claims depend from claim 1 which recites, "wherein said compound inhibits expression of diacylglycerol acyltransferase 2 mRNA by at least 10%" which is relative terminology, the metes and bounds of which cannot be determined without assumption. There is no context in the claim for determining what inhibition of the expression of diacylglycerol acyltransferase 2 mRNA would constitute an inhibition of "at least 10%."

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66, *ibis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43 *bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.